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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,855	10/31/2003	Jens Holm	04305/100M237-US1	9333

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EXAMINER	
TSAY, MARSHA M	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 01/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,855	HOLM ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,19-32,52-57,59,73 and 76-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,19-25,28,52-57,59,73 and 76-92* is/are rejected.

7)☒ Claim(s) *26,27 and 29-32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

This Office Action is in response to Applicants' remarks and amendment received October 17, 2005. Claims 1-17, 19-32, 52-57, 59, 73, 76-92 are pending and currently under examination.

Priority date is November 1, 2002.

Withdrawal of Objections and Rejections

The rejection of claims 1-17, 19-32, 52-57, 59, 73, 76-92 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn.

The rejection of claims 1, 5-6, 9-10, 20-22, 55-56, 59 under 35 U.S.C. 102(b) as being anticipated by Valenta et al. (US 5583046) is withdrawn.

The rejection of claims 1, 5-6, 8-9, 15, 20-24, 52 under 35 U.S.C. 102(b) as being anticipated by Son et al. (1999 Eur J Nutr 38: 201-215) is withdrawn.

The rejection of claims 54, 73 under 35 U.S.C. 102(b) as being anticipated by King et al. (2001 J Immun 166(10): 6057-6065) is withdrawn.

New Objections and Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, 19-22, 52-57, 59, 73, 76-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains

subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims read on a recombinant protein variant wherein the protein variant is a variant of a scaffold protein, wherein the scaffold protein has a three-dimensional folding pattern that is structurally similar to the naturally-occurring allergen. Thus, the claims read on any variant of a protein that has a similar 3-D structure to the natural allergen. The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to protein variants of a scaffold protein that has a similar 3-D structure to the naturally-occurring allergen because the search to find a suitable scaffold protein may be indefinite and the experimentation required is immense.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use

the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case, (1) the amount of experimentation is immense because of the large number of allergens and the large number of potential scaffold proteins for each one; (2) the amount of guidance provided by the specification is minimal since there is no discussion of how closely the structures must match. One of skill in the art would have no idea what structural characteristics are most critical in assessing the similarity between the scaffold protein and the naturally-occurring allergen. Continuing, (3) the specification contains a few working examples of allergen-scaffold pairs, however, one of skill in the art may still need to search indefinitely for a scaffold protein that has a similar structure to the allergen, in addition to the indeterminate number of proteins that may or may not be classified as an allergen; As for the next Wands factor, (4) the nature of the invention is placement of epitopes from allergens onto structurally similar scaffold proteins to minimize the cross-reactivity of the

vaccine to be produced. With regard to Factor (5), the prior art shows the Bet v 1-Mal d 1 (2619) pair (Holm et al. 2001 J Chrom B 756: 307-313; IDS) and the idea of producing modified allergens by preparing hybrids consisting of a small portion of the "guest" allergen of interest and a large portion of a homologous but poorly cross-reacting "host protein...a scaffold," (King et al., paragraph 0036, US 20030039660); (6) the relative level of skill in this art is very high, that of a doctoral level immunologist with several years experience; (7) the predictability of the art is minimal since a priori one of skill in the art would be unable to predict which protein might be structurally similar enough to function as a scaffold. Finally, (8) the claims are enormously broad in the sense that an indeterminate number of proteins may or may not be classified as an allergen.

Based on this analysis, the conclusion that it would require undue experimentation to practice the instant invention is inescapable.

Claims 1-17, 19-22, 52-57, 59, 73, 76-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a recombinant protein variant wherein the protein variant is a variant of a scaffold protein, wherein the scaffold protein has a three-dimensional folding pattern that is structurally similar to the naturally-occurring allergen. *Vas-Cath*

Inc. V. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed."* The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." As stated above, a protein variant of a scaffold protein that has a three-dimensional folding pattern that is structurally similar to the naturally-occurring allergen. However, the skilled artisan cannot necessarily envision all the proteins with a similar 3-D structure to the allergen or which one is suitable for use as a scaffold protein. Furthermore, the number of allergens from which a scaffold protein is to be selected from is indeterminate itself since a particular protein may or may not be classified as an allergen. While the specification does contain a few working examples of allergen-scaffold pairs, it fails to disclose all scaffold proteins to all allergens along with the primary mutations that need to be introduced to the scaffold protein in order to achieve the increased affinity and/or binding capacity to IgE antibodies when compared to the scaffold protein. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or making it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 7-9, 11-14, 19-25, 28, 52-57, 76-78, 90-91 are rejected under 35 U.S.C. 102(a) as being anticipated by Holm et al. (2001 J Chromatography B 756: 307-313; IDS). Holm et al. teach the surface areas shared by the major allergens of birch and apple, Bet v 1 and Mal d 1, was investigated using the 3-D structure model of Bet v 1, primary sequence alignment, and immunochemical methods (p. 308). In the materials and methods section, Holm et al. teach the subcloning of two Mal d 1 genes, 2619 and 2620, their expression, and subsequent purification from DH5α cells (p. 308; claims 55-57, 90-91). Figure 1 illustrates the sequence alignment of the amino acid sequences of Bet v 1.2801, Mal d 1 (2619), and Mal d 1 (2620) compared to 15 other Mal d 1 sequences exhibiting from 57-66% sequence identity (p. 310). On page 30 of the instant specification, Applicants disclose Mal d 1 (2620) is a Bet v 1 scaffold protein and disclose the list of mutations that the at least two primary mutations can be selected from. It can be assessed from Figure 1 that the amino acid sequence of Mal d 1 (2619) contains the amino acid differences E12V, P16A, H40T, and E76K (p. 310; claims 1, 5, 9, 19-25, 28, 76-78, 90-91). Since the recombinant Mal d 1 (2619) meets the limitations of instant claim 1 as a recombinant protein variant of a scaffold protein comprising two or more primary mutations as disclosed in the instant specification, the physical

properties, such as having an increased binding capacity to IgE antibodies as compared to the scaffold protein should be inherently present (claims 1-3, 5, 8, 11, 52-54). At residue 20, recombinant Mal d 1 (2619) contains the amino acid Y, which is a variation from amino acid N in recombinant Mal d 1 (2620) and amino acid K in recombinant Bet v 1 (p. 310; claim 4). In figure 2, Holm et al. teach the surface similarity of Bet v 1.2801, Mal d 1 (2620), and Mal d 1 (2619) (panel I D and E). In panel I.B, Holm et al. disclose the conformational epitope covers a water accessible area of 900 A (p. 311; claims 12-14). Holm et al. also performed immunochemical experiments using a monospecific rabbit antibody raised against natural Bet v 1, wherein rBet v 1 forms a well-defined precipitate while the precipitate of variant Mal d 1 (2620) is less blurred, as compared to the precipitate of variant Mal d 1 (2619) (p. 312, figure 3; claim 7).

Claims 1-17, 19, 53-57, 59, 76-80, 90-92 are rejected under 35 U.S.C. 102(e) as being anticipated by King et al. (US 20030039660). King et al. teach a new approach to prepare modified allergens that have reduced allergenicity but that retain immunogenicity. King et al. teach allergen hybrid proteins comprising a peptide epitope sequence of an allergen protein and a scaffold protein that is structurally homologous to the allergen protein, wherein the hybrid protein has a native conformation and the peptide sequence is present in a surface accessible region of the hybrid protein corresponding to its position in the allergen protein (p. 98 first claim; claims 1, 10). King et al. teach homologous proteins of greater than 30% sequence identity and of similar functions are known to have closely similar three-dimensional structures (p. 4 [0036];

claims 1, 6, 10, 53-54, 80). On page 4, King et al. teach the various peptide epitope sequences, ranging between 6 to 50 amino acids that is present in the modified allergen protein (p. 4 [0043]; claims 1-5, 8-12, 76-79). The recombinant variant allergen is characterized as reducing antibody binding to the peptide epitope sequence by at least 50% in an in vitro assay (p. 99 claim 19; claim 7, 81). King et al. teach a method of designing a hybrid allergen comprising the steps of (a) identifying a solvent exposed surface of an allergen; (b) identifying a protein that is structurally homologous to the allergen; and (c) modifying sequence of the protein that is structurally homologous to the allergen to incorporate a peptide sequence from the solvent exposed surface of the allergen (p. 100 claim 31; claims 12-14, 19). Furthermore, to prepare the recombinant variant allergen, King et al. teach a method for preparing a nucleic acid that encodes an allergen hybrid protein, which comprises introducing a nucleotide sequence encoding a peptide epitope sequence of an allergen protein into a nucleotide sequence encoding a scaffold protein that is structurally homologous to the allergen protein, where the peptide epitope nucleotide sequence is in-frame with the scaffold protein nucleotide sequence (p. 99 claim 21). The nucleotide sequence encoding the scaffold protein is mutated to introduce the nucleotide sequence encoding the peptide epitope sequence or the nucleotide encoding the peptide epitope sequence is introduced by ligating fragments from nucleic acids comprising the nucleotide sequence encoding the peptide epitope sequence and the nucleotide sequence encoding the scaffold protein treated with an endonuclease (p. 100 claims 22-23; claims 15-17). King et al. teach a pharmaceutical composition comprising the modified allergen and a pharmaceutically

acceptable carrier or diluent and wherein the pharmaceutical composition can be administered by various routes for the treatment of allergic conditions (p. 100 claims 29-30; claims 55-57, 59, 90-92).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, 79-89, 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holm et al. (2001 J Chromatography B 756: 307-313). Holm et al. disclose the sequence alignment of the amino acid sequences of Bet v 1.2801, Mal d 1 (2619), and Mal d 1 (2620) compared to 15 other Mal d 1 sequences exhibiting from 57-66% sequence identity (p. 310). Figure 1 illustrates the sequence alignment of the amino acid sequences of Bet v 1.2801, Mal d 1 (2619), and Mal d 1 (2620) compared to 15 other Mal d 1 sequences exhibiting from 57-66% sequence identity (p. 310). In Figure 1, Holm et al. indicate amino acid residues from the Mal d 1 sequences that are identical to Bet v 1.2801 are shown on a red background, while conservative substitutions (V-I-L-M, F-Y-W, S-T-C, E-D, N-Q, K-R-H) are shown on cyan background (p. 310). For example, the rMal d 1 (2619) amino acid sequence contains the variations E12V, P16A, H40T, E76K. Holm et al. also disclose surface similarity analysis between Bet v 1 and the various Mal d 1 isoallergens to illustrate the degree of conserved surface area. In panel I.B, Holm et al. disclose the conformational epitope covers a

water accessible area of 900 A (p. 311). Holm et al. do not teach a protein variant comprising 5 to 12 primary mutations or the various physical differences such as increased binding capacity, CD-spectra deviations, or the solvent accessibility of the primary amino acid residues.

It would have been obvious to a person having ordinary skill in the art to obtain a recombinant protein variant, such as Mal d 1 (2619), which is a variant of a scaffold protein, and introduce additional mutations, such as 5-12, to the sequence because Holm et al. teach the sequence alignment of various Mal d 1 isoallergens, indicating both identical and conservative substitutions, including an idea of the surface-exposed amino acids they have in common with the Bet v 1 allergen (claims 1, 6, 79-82, 92). It would also have been obvious to a person having ordinary skill in the art to realize that the properties, such as degree of binding capacity, CD-spectra deviations, and solvent accessibility of the primary amino acid residues will be dependent on the number of amino acid variations introduced into a Mal d 1 protein or can be selected for based on the surface similarity analysis as disclosed by Holm et al. therefore these limitations are inherent to the specific recombinant protein that is created and/or obtained from the many variants that are disclosed by Holm et al. (claims 1, 6, 79-82, 92).

Claims 26-27, 29-32 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is 571-272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

December 29, 2005

ROBERT A. WAX
PRIMARY EXAMINER